9-1-2023

Development of New Synthetic Routes for Ebselen in Pursuit of the First Synthesis of Ebtellur

Elijah J. Kellner
Winona State University

Creed D. Poppler
Winona State University

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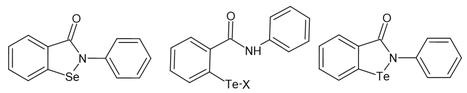
Elijah J Kellner, Creed D Poppler, and Joseph K West
Department of Chemistry, Winona State University

Abstract

Ebselen, *N*-phenyl-1,2-benzoisoselenazol-3(*2H*)-one, an established anti-oxidant and cytoprotective agent, has been assessed for an array of pharmaceutical applications in treating a multitude of disorders and maladies. It has further been identified as an anti-microbial and anti-viral agent against multiple infectious agents and has even been FDA-approved for a variety of these applications. While ebselen has captured pharmaceutical interest, its tellurium analogue, ebtellur, has yet to be successfully obtained, and in only one case was an attempt to obtain ebtellur reported. We have developed multiple new synthetic routes specifically targeting the first synthesis of ebtellur and discuss the viability of each pathway herein.

Introduction

Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) is a modern pharmaceutical compound which is currently undergoing clinical trials to assess its potential in preventing and treating disorders such as cancer, stroke, arthritis, and cardiovascular disease. Ebselen has also shown promise in use for treating bipolar disorder and exhibits strong anti-viral and anti-bacterial properties. As an anti-viral agent ebselen has been shown to inhibit SARS-CoV-2 replication and transcription when used in conjunction with disulfiram and remdesivir and to inhibit the hepatitis C virus through helicase deactivation. Additionally, ebselen has been shown *in vitro* to mimic the activity of glutathione peroxidase; an enzyme involved with antioxidant activity in the body. This similarity allows for ebselen to be used for purposes such as bioimaging and fluorescence analysis. Given the success of ebselen in the pharmaceutical industry, the investigation of analogues of the drug poses interest. One such analogue is ebtellur, which differs from ebselen with the substitution of tellurium in place of selenium. Thus far, there has been no reported successful synthesis of this analogue. Previous attempts to synthesize ebtellur have provided tellurohalide complexes in lieu of a ring closure. This project aims to develop and inspect novel ebselen routes which also enable the first synthesis and isolation of ebtellur. These routes include variations such as ligand lithiation to guide ring formation and previously unused chalcogen sources, namely tellurium and selenium tetrachloride, to bind to the lithiated ligand. Ring formation will be followed by reduction of the chalcogen to remove remaining halogens. Upon reduction the desired molecules, ebselen and ebtellur, will have been formed. The formation of intermediates, side products, and products will be characterized through mass spectrometry, ^{1}H , ^{77}Se, and ^{125}Te NMR, X-ray diffraction, and elemental analysis.



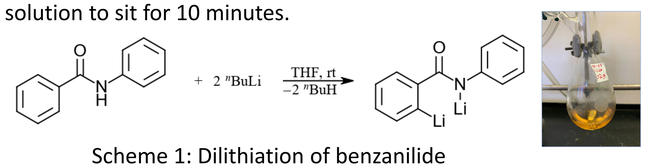
X = Cl, Br, I

Figure 1: Chemical structures of ebselen (left), tellurohalide complexes (center) and ebtellur (right)

Methods and Materials

Dilithiation of benzanilide

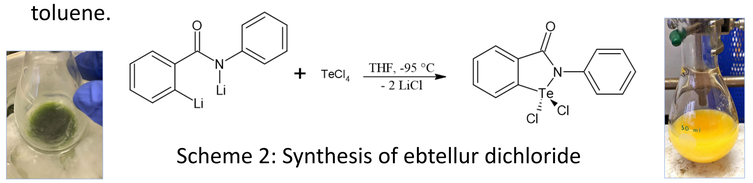
1. Benzanilide (0.247 g) was added to a Schlenk flask and cycled flask under N_2 and vacuum.
2. Dried THF (~8 mL) was added via needle.
3. n-butyllithium (1 mL) was added to solution dropwise via needle (10 minutes).
4. Allowed solution to sit for 10 minutes.



Scheme 1: Dilithiation of benzanilide

Synthesis of ebtellur dichloride

1. Tellurium tetrachloride (0.337 g) was added to a Schlenk flask under an inert atmosphere.
2. Dried THF (~10 mL) was added via needle.
3. Solution was placed into a liquid N_2 /acetone bath.
4. Solution of lithiated benzanilide was added to tellurium tetrachloride solution dropwise via needle (10 minutes).
5. Solution was warmed to room temperature with occasional venting through Schlenk line.
6. Solution was evaporated in vacuo and resulting solids were filtered using toluene.



Scheme 2: Synthesis of ebtellur dichloride

Results

Dilithiation and combination of tellurium tetrachloride with benzanilide resulted in the formation of a tellurium containing ring and dimer linked through the benzanilide oxygen and tellurium chlorides.

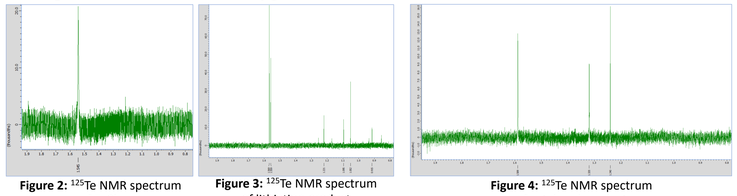
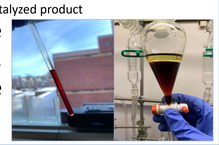


Figure 2: ^{125}Te NMR spectrum of $TeCl_4$

Figure 3: ^{125}Te NMR spectrum of lithiation product

Figure 4: ^{125}Te NMR spectrum of catalyzed product

A catalyzed attempt utilizing potassium tellurocyanate yielded ^{125}Te NMR peaks at 1.59, 1.32, and 1.24 ppt. Products are believed to be ditellurides due to these peak ranges and the product color.



A similar attempt using chloroform as the solvent gave crystals and a powder which appear to identical compounds. This was determined through ^{1}H NMR spectroscopy and melting point determination. XRD showed the crystals to be cocrystallized benzanilide and tellurium tetrachloride.

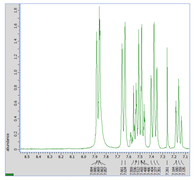


Figure 5: ^{1}H NMR spectrum of benzanilide

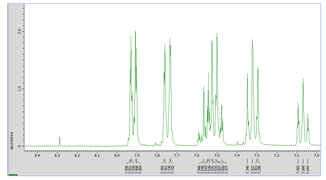


Figure 6: ^{1}H NMR spectrum of chloroform reaction crystals

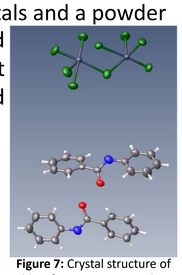
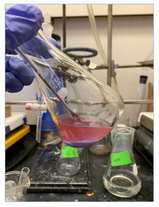


Figure 7: Crystal structure of chloroform reaction product

A solvent free reaction of benzanilide and tellurium tetrachloride resulted in the formation of an ionic species, which was evidenced by the product color and the color change seen during drying with magnesium sulfate.



Discussion

The reactions which produced the suspected dimer and ionic species will likely not yield ebtellur, and thus these reactions will require tailoring of starting materials and methods. The catalyzed tellurocyanate route requires further investigation to characterize the products. Trials which failed to yield products also require further reaction tailoring and testing to identify other possible ebtellur routes.

The formation of the tellurium dimer bound to the benzanilide oxygen from the lithiation route likely occurred because of electron delocalization between the nitrogen and oxygen on benzanilide after the lithiation step, which allowed the oxygen to also react with tellurium tetrachloride. The formation of ions during the solvent free reaction may have occurred because the temperature required to melt benzanilide and allow the reaction to occur may have been high enough to also partially decompose portions of the starting materials or allow for other energetically demanding reactions to occur.

Conclusions

Several routes and attempts to synthesize the tellurium containing analogue of the bioactive molecule ebselen, ebtellur, are reported in this project. New tellurium sources and routes were chosen to avoid the formation of previous dead-end products. The novel lithiation route using tellurium tetrachloride yielded a dimer containing two benzanilide and two tellurium centers. The solvent free attempt produced an ionic species which is incompatible with ebtellur formation. The catalyzed tellurocyante route is believed to have yielded ditellurides. Other attempted routes require further investigation to determine product identities and route feasibilities. Future work will focus on known issues and investigate similar reactions with new tellurium sources.

References

(1) Jaromin, A.; Zarnowski, R.; Piętka-Ottlik, M.; Andes, D. R.; Gubernator, J. Topical Delivery of Ebselen Encapsulated in Biopolymeric Nanocapsules: Drug Repurposing Enhanced Antifungal Activity. *Nanomed.* **2018**, *13* (10), 1139–1155. https://doi.org/10.2217/nnm-2017-0337.

(2) Mugesh, G.; Singh, H. B. Synthetic Organoselenium Compounds as Antioxidants:Glutathione Peroxidase Activity. *Chem. Soc. Rev.* **2000**, *29* (5), 347–357. https://doi.org/10.1039/A908114C.

(3) Mukherjee, S.; Weiner, W. S.; Schroeder, C. E.; Simpson, D. S.; Hanson, A. M.; Sweeney, N. L.; Marvin, R. K.; Ndjomou, J.; Kolli, R.; Isailovic, D.; Schoenen, F. J.; Frick, D. N. Ebselen Inhibits Hepatitis C Virus NS3 Helicase Binding to Nucleic Acid and Prevents Viral Replication. *ACS Chem. Biol.* **2014**, *9* (10), 2393–2403. https://doi.org/10.1021/cb500512z.

(4) Chen, T.; Fei, C.-Y.; Chen, Y.-P.; Sargsyan, K.; Chang, C.-P.; Yuan, H. S.; Lim, C. Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir. *ACS Pharmacol. Transl. Sci.* **2021**, *4* (2), 898–907. https://doi.org/10.1021/acsptsci.1c00022.

(5) Zhang, J.; Yang, L.; Wang, Y.; Cao, T.; Sun, Z.; Xu, J.; Liu, Y.; Chen, G. Ebselen-Agents for Sensing, Imaging and Labeling: Facile and Full-Featured Application in Biochemical Analysis. *ACS Appl. Bio Mater.* **2021**, *4* (3), 2217–2230. https://doi.org/10.1021/acsabm.0c01561.

(6) Engman, L.; Hallberg, A. Expedient Synthesis of Ebselen and Related Compounds. *J. Org. Chem.* **1989**, *54* (12), 2964–2966. https://doi.org/10.1021/jo00273a035.

(7) Engman, L.; Persson, J. Mild Reduction of Tellurium(IV) and Selenium(IV) Compounds by Sodium Ascorbate. *Synth. Commun.* **1993**, *23* (4), 445–458. https://doi.org/10.1080/00397919308009800.

Acknowledgments

I would like to thank the Winona State Chemistry Department for providing the space and supplies to conduct this project, the Winona State Grants & Sponsored Projects Office for supporting this work through the Undergraduate Student Research & Creative Projects Grant and the Undergraduate Student Research & Creative Presentations Travel Support Grant, and the Winona State Student Senate for funding the lodging for this presentation.